MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 28, 2005

FROM: Ann Corken Mackey, R.Ph., M.P.H.
Postmarketing Safety Evaluator
Office of Drug Safety
Division of Drug Risk Evaluation, HFD-430

THROUGH: Mark Avigan, M.D., C.M., Director
Div. of Drug Risk Evaluation, HFD-430

TO: Solomon Iyasu, MD, MPH., Team Leader
Division of Pediatric Drug Development, HFD-960
Office of Counter-Terrorism and Pediatric Drug Development, HFD-950

SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review (PID# D040346)
Anagrelide hydrochloride (Agrylin) NDA# 20-333
Pediatric Exclusivity Approval Date: May 25, 2004

Executive Summary

As requested by the Office of Counter-Terrorism and Pediatrics, we reviewed the pediatric adverse events in association with the use of anagrelide hydrochloride (Agrylin) in children aged 16 years and younger. The time period of interest was the one-year period (the search period is expanded to 13 months to allow for the time lag needed to collect 12 months of data) following FDA Pediatric Exclusivity approval, May 25, 2004 through June 25, 2005.

For the 12-month time period after pediatric exclusivity was granted, we identified no adverse events in children 16 years of age and younger. We will continue to monitor adverse events for a second year because there is insufficient evidence to conduct a meaningful analysis.

AERS Search Results: Anagrelide hydrochloride (Agrylin)

AERS Search Dates: Searches for U.S. and foreign cases during the following time periods, (1) March 14, 1997 (approval date) to June 25, 2005, and (2) May 25, 2004 (pediatric exclusivity date) to June 25, 2005.

A. Adverse events from marketing approval date, March 17, 1997 to June 25, 2005:

1. Raw counts of reports: Table 1 (parentheses denote U.S. origin report counts)

	All reports (US)	Serious (US)	Death (US)
All ages	456 (336)	432 (319)	27 (12)
Adults (≥17)	454 (335)	431 (319)	27 (12)
Peds (0-16)	2 (1)	1 (0)	0 (0)

Figure 1: Reporting trend for pediatric reports from approval date:

Year	Report count
1996	1
1999	1*

* This foreign case involved adverse effects in a baby whose mother took anagrelide (2 mg/day for approximately 9 months) during pregnancy (indirect exposure). Shortly after delivery, the baby developed necrotizing enterocolitis and his platelets dropped to 17, requiring platelet support. The baby was in a special care unit; per follow up, the baby had left the hospital. (The label states that anagrelide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.)

2. Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups (underscore denotes unlabeled events).

All ages: Headache (47), palpitations (44), dyspnoea (29), cardiac failure congestive (25), diarrhoea (25), asthenia (21), anaemia (20), chest pain (20), oedema peripheral (20), myocardial infarction (19), pancreatitis (18), tachycardia (18), vomiting (17), abdominal pain (16), nausea (16), dizziness (15), pyrexia (14), haemoglobin decreased (13), platelet count increased (13), pleural effusion (13)

Adults: Headache (46), palpitations (44), dyspnoea (29), cardiac failure congestive (25), diarrhoea (25), asthenia (21), anaemia (20), chest pain (20), oedema peripheral (20), myocardial infarction (19), pancreatitis (18), tachycardia (18), vomiting (17), abdominal pain (15), nausea (16), dizziness (15), pyrexia (14), haemoglobin decreased (13), platelet count increased (13), pleural effusion (13)

Peds: Abdominal pain (1), complications of maternal exposure to therapeutic drugs (1), enteritis necroticans (1), headache (1), premature baby (1)

B. From Pediatric Exclusivity approval date through AERS cut-off date (June 25, 2005):

1. Raw counts of reports: Table 2

	All reports (US)	Serious (US)	Death (US)
All ages	81 (29)	80 (29)	10 (1)
Adults (≥17)	81 (29)	80 (29)	10 (1)
Peds (0-16)	0 (0)	0 (0)	0 (0)

2. Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups including identifying events not previously described in the label (underscore denotes unlabeled events).

   All ages: Haemoglobin decreased (8), palpitations (7), platelet count increased (7), anaemia (6), chest pain (6), drug exposure during pregnancy (6), asthenia (5), myocardial infarction (5), vertigo (5), vomiting (5), abdominal pain (4), constipation (4), diarrhoea (4), headache (4), hyperphosphataemia (4), insomnia (4), myelofibrosis (4), nausea (4), white blood cell count increased (4), abdominal discomfort (3)

   Adults: Haemoglobin decreased (8), palpitations (7), platelet count increased (7), anaemia (6), chest pain (6), drug exposure during pregnancy (6), asthenia (5), myocardial infarction (5), vertigo (5), vomiting (5), abdominal pain (4), constipation (4), diarrhoea (4), headache (4), hyperphosphataemia (4), insomnia (4), myelofibrosis (4), nausea (4), white blood cell count increased (4), abdominal discomfort (3)

   Peds: There were no adverse event reports involving children 16 years of age or younger.

Postmarketing hands-on review of all peds adverse event reports from all sources received during the one-year after a drug receives pediatric market exclusivity.

There were no adverse event reports involving children 16 years of age or younger.

Summary

For the 12-month time period after pediatric exclusivity was granted, we identified no adverse events in children 16 years of age and younger. We will continue to monitor adverse events for a second year because there is insufficient evidence to conduct a meaningful analysis.

Ann Corken Mackey 6/28/05

_____

Ann Corken Mackey, R.Ph., M.P.H.

Concur:
Lanh Green 6/28/05

_____

Lanh Green, Pharm.D., M.P.H.

Appendix

Standard Searches:

A. Adults (17 yrs and above)
   1. All outcomes from AP date (no set criteria)
   2. Serious outcomes from AP date
   3. Death as an outcome from AP date
   4. All outcomes from PE date to present or any desired date
   5. Serious outcomes from PE date to present or any desired date
   6. Death as an outcome from PE date to present or any desired date

B. Ages 0-16 yrs ONLY
   1. Same as above 1-6
   2. Retrieve case reports for hands-on review

Standard Printouts for Attachments:

A. Adults (17 yrs and above)
   1. Frequency counts of all preferred terms (PT) in cases
   2. Frequency counts of all PT in cases with serious outcomes
   3. Frequency counts of all PT in cases with death as an outcome
   4. Frequency counts of cases by Gender and ages

B. Ages 0-16 yrs ONLY
   Same as above 1-4

Drug Product Information

Limitations of the Adverse Event Reporting System (AERS)

AERS collects reports of adverse events from health care professionals and consumers submitted to the product manufacturers or directly to the FDA. The main utility of a spontaneous reporting system, such as AERS, is to identify potential drug safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ann Corken
6/28/05 04:49:02 PM
PHARMACIST

Mark Avigan
6/28/05 05:45:05 PM
DRUG SAFETY OFFICE REVIEWER